

## REMARKS

In response to the Office Action of August 6, 2003, Applicants have amended the claims, which when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

In the first instance, Applicants through the undersigned, thank Examiners Collins and Nelson for their time and consideration in granting a personal interview with the undersigned and representatives from CropDesign, N.V. on October 14, 2003. Applicants further thank Examiner Collins for the helpful suggestions provided during the course of the interview, where it was indicated that the presently amended claims would be favorably considered.

Applicants acknowledge the withdrawal of claims 47-49.

Claim 1 has been objected to because part (a) does not agree in number with part (ab). As presently amended, claim 1 recites "a DNA molecule" in each of elements (a) through (d). Withdrawal of the objection of claim 1 is respectfully requested.

Claims 1 and 5, 6-10, and 13-23 dependent thereon, remain rejected and claim 50 is newly rejected under 35 U.S.C. § 112, first paragraph, as allegedly violative of the written description requirement. The Examiner's position is that an isolated DNA molecule encoding a cell cycle-interacting protein that binds to a cyclin-dependent kinase having a PPTALRE motif is not sufficient to describe the structure of the nucleic acid sequences that encode functional polypeptides. Further, the Examiner has posited that Applicants have not disclosed what structural characteristics of SEQ ID NOs: 7 and 8 are correlated with the specific function(s) of SEQ ID NOs: 7 and 8. Applicants also observe the Examiner's comments on the Interview Summary Record (Paper No. 15, dated October 14, 2003) where the Examiner has stated: "Need

to correlate conserved structural features of disclosed sequences with conserved structural features of known functional HAL sequences as evidence of functionality.”

In response to the rejection of claims 1 and 5, and claims 6-10 and 13-23, dependent thereon, Applicants have amended the claims as follows. Claim 1 has been amended to recite:

“[a]n isolated DNA molecule encoding a cell cycle interacting protein or encoding an immunologically active and/or functional fragment thereof, wherein said cell cycle interacting protein binds to a cyclin dependent kinase (CDK) having a PPTALRE cyclin binding motif and wherein said isolated DNA molecule is selected from the group consisting of: (a) a DNA molecule comprising a nucleotide sequence encoding at least the mature form of a protein comprising the amino acid sequence as set forth in SEQ ID NO: 8; (b) a DNA molecule comprising the nucleotide sequence as set forth in SEQ ID NO: 7;

(c) a DNA molecule comprising a nucleotide sequence hybridizing with the complementary strand of a nucleotide sequence as defined in (a) or (b) under stringent hybridization conditions of hybridization in 4X SSC at 65° C, followed by washing in 0.1X SSC at 65° C, or hybridization in 50% formamide, 4X SSC at 42° C, followed by washing in 0.1X SSC; wherein the nucleotide sequence encodes a protein comprising amino acids 96-118 of SEQ ID NO:8, allowing up to four mismatches, and (d) a DNA molecule comprising a nucleotide sequence encoding a protein having an amino acid sequence at least 50 % identical to the amino acid sequence encoded by the nucleotide sequence of (a) or (b) wherein the nucleotide sequence encodes a protein comprising amino acids 96-118 of SEQ ID NO:8, allowing for up to four mismatches.

Support for the amendment to claim 1 may be found throughout the specification, e.g., SEQ ID NO:8 and page 19. In response to the Examiner's request that Applicants need to correlate conserved structural features of disclosed sequences with conserved structural features of known functional HAL3 sequences as evidence of functionality, Applicants respectfully submit the following: Claim 1 has been amended to recite that the nucleotide sequence encodes a protein comprising amino acids 96-118 of SEQ ID NO:8, allowing for up to four mismatches. Basis for defining this stretch in particular may be derived from SEQ ID NO:8 and homologous sequences known at the filing date, namely the yeast HAL3p and SIS2 proteins, and the U80192 protein from *Arabidopsis*. (See *infra*, page 16, for a description of U80192). The two yeast sequences are identical to each other. See the alignments in Exhibit A. Further, the two yeast sequences are clearly different from the protein encoded by Applicants' SEQ ID NO:8. In particular the yeast sequence differs in 5 amino acids in the region spanning residues 96-118 of SEQ ID NO:8. See the alignments submitted herewith as Exhibit B. Applicants' VB89 corresponds to the ORF of SEQ ID NO:8, Hal3b corresponds to the sequence of GenBank Accession Number U80192, HAL3p and SIS2 are respectively the sequences from GenBank Accession Numbers AAB35308 and U01878. When the 23 amino acid stretch of SEQ ID NO:8 (now recited in claim 1 as amino acids 96-118 of SEQ ID NO:8) was used in a BLAST search, no sequences came up that were deposited before the date of Applicants' filing or that did not relate to HAL3.

Applicants respectfully submit therefore, that one skilled in the art having the present application and the available HAL3p, SIS2 and V80192 sequences in hand, could have reasonably derived the 23 amino acid structural feature presently recited in the claims comprising up to four mismatches. Applicants respectfully submit that as presently amended

claim 1 is not unduly broad in scope. Claim 1 does not cover any prior art sequences, since the prior art sequence from yeast has five mismatches in the 23 amino acid region defined therein and there is only 10% overall homology between the yeast and plant Hal3 sequences.

Thus, as presently amended, claims 1, 5, 6-10, and 13-23 dependent thereon, presently correlate conserved structural features of SEQ ID NO:8 with conserved structural features of known functional HAL sequences as requested by the Examiner. Withdrawal of the rejection of claims 1, 5, 6-10, and 13-23 under the written description requirement of 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

Claims 1, 10, and 19 remain rejected under 35 U.S.C. §112, second paragraph, as being indefinite in recitation of "cell cycle interacting protein" for reasons stated in the previous office action of January 29, 2003. Although claim 1 was amended to recite an isolated DNA molecule encoding a cell cycle-interacting protein that binds a cyclin-dependent kinase having a PPTALRE motif, such an amendment does not overcome the rejection. According to the Examiner as set forth on page 5 of the office action, many different types of proteins may bind a cyclin-dependent kinase to produce different types of effects on the cell cycle. In order to advance prosecution of this application, and as described above, claim 1 presently recites a conserved structural feature found in the yeast functional HAL sequence, which sequence was known at the time of filing the present application. *See* specification, page 72. Thus, withdrawal of the rejection of claims 1, 10, and 19 under 35 U.S.C. 112, second paragraph, is warranted.

Claim 18 remains rejected and claim 50 has been newly rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite in the recitation of "environmental stress" for those reasons set forth in the previous office action. In the previous office action (Office Action of January 29, 2003, page 6), the Examiner stated that it is unclear what types of stress are

encompassed by the claim, as any aspect of the environment can impose a stress on a plant."

Applicants direct the Examiner to page 34, lines 5-8 of the specification where it is disclosed that "overproduction of the cell cycle interacting protein of the invention enhances growth and results in cell division to be less sensitive to an arrest caused by environmental stress such as salt, nutrient deprivation, drought, chilling and the like." Claims 18 and 50 are presently amended to recite in relevant part: "wherein the plant is less sensitive to salt, nutrient deprivation, drought, or chilling compared to a corresponding wild type plant." Withdrawal of the rejection of claims 18 and 50 under 35 U.S.C. §112, second paragraph is therefore respectfully requested.

Claim 5 remains rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter for the reasons set forth in the previous office action. In order to overcome the rejection, the Examiner has suggested claim 5 be amended to recite that the nucleic acid molecule is isolated. Amended claim 5 presently recites in relevant part: "an isolated nucleic acid molecule of at least 15 nucleotides..." Withdrawal of the rejection of claim 5 under 35 U.S.C. § 101 is therefore warranted.

Claims 1, 5-10 and 13-23 remain rejected and claim 50 is newly rejected under 35 U.S.C. § 101, as allegedly not supported by either a specific and substantial asserted utility or a well established utility, for the reasons set forth in the previous office action. In response to Applicants' arguments presented in the previously submitted amendment, the Examiner has now asserted that: "as the prior art teaches that general structural homology between amino acid sequence is not always predictive of functional homology, a showing that SEQ ID NO:8 exhibits specific structural homology to HAL3 in regions known to be essential for HAL3 function would be necessary in order to demonstrate a utility for SEQ ID NO:8 based on homology to HAL3. Such a showing is particularly crucial given that the specification discloses the DNA sequence of

SEQ ID NO:7 as encoding a polypeptide corresponding to a partial open reading frame, as the additional amino acids corresponding to the remainder of the open reading frame could be required for protein function."

Applicants respectfully submit that SEQ ID NO:7 encodes a full length protein and is not a partial open reading frame. As described in the specification at Example 4, when Vb89 was used to screen the publicly available data bases, an overall perfect homology with HAL3 was found. It was the HAL3 sequence deposited in the database at the time the application was first filed that comprised a partial cDNA, not Applicants' VB89. Applicants further submit the following history concerning Applicants' VB89 clone (SEQ ID NO:8). The truncated HAL3 clone present in the GenBank database under accession no U80192 was deposited on December 12, 1996. The stop codon of the sequence was missing and it was not yet known that there were 2 HAL3 genes in *Arabidopsis*. When the present application was first filed on December 17, 1998, Applicants had a complete HAL3b sequence (VB89, SEQ ID NO:8). On July 7, 1999, the full length sequence of Hal3A was deposited in GenBank (AF166262) by Culianez et al. On August 18, 1999, Culianez et al. updated the sequence of HAL3b by adding the stop codon. On January 5, 2000, the Espinosa-Ruiz et al. paper was published in *The Plant Journal* 20(5):529-539, which contained the sequences of both HAL3a and HAL3b.

Applicants repeat, reassert, and incorporate by reference, the discussion above concerning the presently amended claims reciting a conserved structural feature from the functioning HAL sequence of yeast. Thus, Applicants' claims presently recite conserved structural features of SEQ ID NO:8 which correlate with conserved structural features of known

functional HAL sequences. Withdrawal of the rejection of Claims 1, 5-10, 13-23 and 50 under 35 U.S.C. § 101 is therefore warranted.

Claims 1 and 5-10 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by DeVeylder et al. (1997) *FEBS Letts.* 412:446-452, for reasons set forth in the previous office action. In Applicants' amendment filed May 22, 2003, it was argued that amendment of the claims to recite specific hybridization conditions should overcome the rejection since the DNA sequence taught by DeVeylder et al. would not hybridize to the claimed DNA molecules under the conditions recited. In response to Applicants' position asserted in the previous amendment, the Examiner has posited that the recitation of specific hybridization conditions does not overcome the rejection since the DNA sequence taught by DeVeylder et al. read on element (af) of claim 1. That is, the DNA sequence taught by DeVeylder et al. would be obtainable by screening an appropriate library under the stringent conditions recited in element (ac) of claim 1, with a probe having at least 17 consecutive nucleotides of the sequence set forth in SEQ ID NO:17(*sic*, SEQ ID NO:7). According to the Examiner, the DNA sequence taught by DeVeylder et al. encodes a polypeptide that binds Cdc2bAt, as does the polypeptide of SEQ ID NO:8. Further, although the full length sequence taught by DeVeylder et al. may not hybridize to the full length sequence of SEQ ID NO:7 under the recited conditions, the DNA sequence of DeVeylder et al. would necessarily contain a region that would hybridize to at least 17 consecutive nucleotides of the sequence set forth in SEQ ID NO:7 where the 17 consecutive nucleotides correspond to the region of SEQ ID NO:7 that encodes the amino acid of SEQ ID NO:8 that mediate the binding of SEQ ID NO:8 to Cdc2bAt. Finally, the Examiner notes that the claims continue to be directed to a nucleotide sequence encoding at least the domain binding to CDKs of the protein encoded by the nucleotide sequence of any one of elements (aa) to (ad).

The Examiner has maintained that the DNA sequence taught by DeVeylder et al. would inherently encode at least the domain binding to CDKs, since CKS proteins are known to bind to CDKs.

In response to the rejection and in order to advance prosecution of this application, claim 1 has been amended so that elements (ae) and (af) are deleted. Further, submitted herewith as Exhibit C is a nucleotide sequence alignment of the CKS1 gene disclosed in DeVeylder et al. and Applicants' SEQ ID NO:7. Alignment of both sequences show that there is very little homology between the two sequences – the sequences have only five (5) nucleotides in common. Withdrawal of the rejection of claims 1 and 5-10 under 35 U.S.C. 102(b) is therefore warranted.

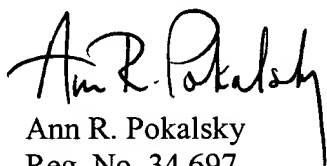
Claims 1, 5-10 and 13-23 remain rejected and claim 50 is newly rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Doerner et al. (1996) *Nature* 380:520-523, in view of DeVeylder et al. (1997) *FEBS Letts.* 412:446-452 for reasons of record in the previously issued office action of January 29, 2003. In the office action of January 29, 2003, Doerner et al. was cited for teaching a method for the production of transgenic plants comprising introducing a DNA sequence encoding an *Arabidopsis* Cyc1At cyclin cell cycle interacting protein into the genome of an *Arabidopsis* plant cell and regenerating an *Arabidopsis* plant. Doerner et al. is also cited for teaching that transgenic *Arabidopsis* plants produced by the method exhibit an increase in root growth rate. The teaching provided by DeVeylder et al. is described above and is directed to a CKS1 gene. Neither reference, taken alone or in combination, even remotely suggests Applicants' claimed HAL3 gene, vectors comprising the gene, host cells, methods of producing the corresponding HAL3 protein, transgenic plants comprising the HAL3 gene and methods of producing such transgenic plants. Absent a suggestion in either DeVeylder et al. or Doerner et al. for the invention as presently recited in claims 1, 5-10, 13-23, and 50, the present



invention is not obvious. Withdrawal of the rejection of claims 1, 5-10, 13-23 and 50 under 35 U.S.C. § 103(a) is therefore respectfully requested.

In view of the foregoing remarks and amendments to the claims, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited. The Examiner is invited to telephone the undersigned in order to resolve any issues that may remain, e.g., by Examiner's amendment.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Ann R. Pokalsky". The signature is fluid and cursive, with the first name "Ann" and last name "Pokalsky" clearly distinguishable.

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```
needle Sc HAL3 SIS2.txt
#####
# Program: needle
# Rundate: Tue Dec 02 14:13:08 2003
# Align_format: srspair
# Report_file: outfile
#####
#=====
#
# Aligned_sequences: 2
# 1: HAL3p_Sc
# 2: SIS2_Sc
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 562
# Identity: 562/562 (100.0%)
# Similarity: 562/562 (100.0%)
# Gaps: 0/562 ( 0.0%)
# Score: 2924.0
#
#
#=====

HAL3p_Sc      1 mtavastsgkqdadhngsiecprfsrggkeilldhedakgkdsiinspvs      50
                |||
SIS2_Sc      1 mtavastsgkqdadhngsiecprfsrggkeilldhedakgkdsiinspvs      50
                |||

HAL3p_Sc     51 grqsisptlsnatttttksimnatgtsgavvsntpepglkrvpavtfsdl      100
                |||
SIS2_Sc     51 grqsisptlsnatttttksimnatgtsgavvsntpepglkrvpavtfsdl      100
                |||

HAL3p_Sc    101 kqqqkqdsltqlkndsertkspnsnpapvsnsipgnhavipnhtntsrtt      150
                |||
SIS2_Sc    101 kqqqkqdsltqlkndsertkspnsnpapvsnsipgnhavipnhtntsrtt      150
                |||

HAL3p_Sc    151 qlsgsplvnemkdydpkkkdsalkivdtmkpdkimatstpisrennkvt      200
                |||
SIS2_Sc    151 qlsgsplvnemkdydpkkkdsalkivdtmkpdkimatstpisrennkvt      200
                |||

HAL3p_Sc    201 kaptsitlrkedaqdgannvsgqinvrstpeetpvkqsvipsiipkrens      250
                |||
SIS2_Sc    201 kaptsitlrkedaqdgannvsgqinvrstpeetpvkqsvipsiipkrens      250
                |||

HAL3p_Sc    251 knldprlpqddgklhvlfgatgslsvfkikpmikkleeiygrdrisiqvi      300
                |||
SIS2_Sc    251 knldprlpqddgklhvlfgatgslsvfkikpmikkleeiygrdrisiqvi      300
                |||

HAL3p_Sc    301 ltqsatqffeqrytkkiiksseklnkmsqyestpatpvtptpgqcnmaq      350
                |||
SIS2_Sc    301 ltqsatqffeqrytkkiiksseklnkmsqyestpatpvtptpgqcnmaq      350
                |||

HAL3p_Sc    351 velpphiqlwtdqdewdawkqrt dpvlhielrrwadilvvapltantlsk      400
                |||
SIS2_Sc    351 velpphiqlwtdqdewdawkqrt dpvlhielrrwadilvvapltantlsk      400
                |||

HAL3p_Sc    401 ialglcdnlltsvirawnpsypillapsmvsstfnsmmtkkqlqtikeem      450
                |||
SIS2_Sc    401 ialglcdnlltsvirawnpsypillapsmvsstfnsmmtkkqlqtikeem      450
                |||

HAL3p_Sc    451 swvtvfkpsekvmddingdiglggmdwneivnkivmklggypknneedd      500
                |||
SIS2_Sc    451 swvtvfkpsekvmddingdiglggmdwneivnkivmklggypknneedd      500
                |||
```

```

                                needle Sc HAL3 SIS2.txt
HAL3p_Sc      501 dedeeedddeeedtedknennnnnddddddddddadeded          550
                |||||
SIS2_Sc       501 dedeeedddeeedtedknennnnnddddddddddadeded          550
                |||||

HAL3p_Sc      551 eaetpgiidkhq           562
                |||||
SIS2_Sc       551 eaetpgiidkhq           562

```

##-----

##-----

## needle VB89 SchAL3p.txt

```
#####
# Program: needle
# Rundate: Tue Dec 02 14:17:25 2003
# Align_format: srspair
# Report_file: outfile
#####
#=====
#
# Aligned_sequences: 2
# 1: VB89_2
# 2: HAL3p_Sc
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 568
# Identity:      74/568 (13.0%)
# Similarity:    123/568 (21.7%)
# Gaps:          373/568 (65.7%)
# Score: 314.5
#
#
#=====
```

VB89_2	1		0
HAL3p_Sc	1	mtavastsgkqdadhnqsiecprfsrggkeilldhedakgkdsiinspvs	50
VB89_2	1		0
HAL3p_Sc	51	grqsisptlsnatttttksimnatgtsgavvsntpepglkrvpavtfsdl	100
VB89_2	1		0
HAL3p_Sc	101	kqqqkqdsלטqlkndsertkspnsnpapvsnsipgnhavipnhtntsrtt	150
VB89_2	1		0
HAL3p_Sc	151	qlsgsplvnemkdydpkkksalkivdtmkpdkimatstpisrennkvt	200
VB89_2	1		0
HAL3p_Sc	201	kaptsitlrkedaqdaqnnvsgqinvrstpeetpvkqsvipsiipkrens	250
VB89_2	1		19
HAL3p_Sc	251	knldprlpqddgklhvlfgatgslsvfkikpmikkleeiygrdri-----	295
VB89_2	20	GSVASIKFSNLCHCFSEWAEVKAVASKSSLN----FVDKPS-----	56
HAL3p_Sc	296	-siqviltqsatqffeerytkkiiksseklnkmsqvestpatpvtptpgq	344
VB89_2	57	-----LPQNVTLTYTDEDEWSSWNKIGDPVLHIELRRWADVMIAPLS	98
HAL3p_Sc	345	cnmaqvvelpphiqlwtgdqewdawkqrtdpvlhielrrwadilvvaplt	394
VB89_2	99	ANTLAKIAGGLCDNLLTCIVRAWDYSKPLFVAPAMNTLMWNNPFTERHL-	147
HAL3p_Sc	395	antlskialglcdnlltsvirawnsypillapsmvsstfnsmttkkqlq	444
VB89_2	148	VLLDELG-ITLIPPIKKKLAC-GDYNGGAMAEPsLIYSTV--RLFWESQA	193
HAL3p_Sc	445	tikeemswvtvfkpsekvmddingdiglggmmdwneivnkivmklgyypkn	494

needle VB89 SCHAL3p.txt

VB89_2	194 RKQRDGTS	201
	.... ...	
HAL3p_Sc	495 neeedddedeeeddddeeedtedknennnddddddddddddddddddd	544
VB89_2	202	201
HAL3p_Sc	545 ddededeaetpgiidkhq	562

#-----  
#-----

EMBOSS-GUI v1.13: output from needle

## needle: output

Output file: outfile [right click to save]

```
#####
# Program: needle
# Rundate: Thu Sep 11 18:02:11 2003
# Align_format: srspair
# Report_file: outfile
#####
=====
#
# Aligned_sequences: 2
# 1: CKS1- FROM DE VEYDER ET AL.
# 2: HAL3
# Matrix: EDNAFULL
# Gap_penalty: 95.0
# Extend_penalty: 9.5
#
# Length: 863
# Identity:      5/863 ( 0.6%)
# Similarity:    5/863 ( 0.6%)
# Gaps:          856/863 (99.2%)
# Score: 17.0
#
#=====
CKS1      1 atgggtcagatccaatactccgagaaatacttcgatgacactttcgaata      50
                                           0
HAL3      1
CKS1      51 caggcacgtcgttctctcctcctgaagtcgctaaacttcttccaagaatc      100
                                           0
HAL3      1
CKS1      101 gtcttctctccgaaaacyaatggcgagcgataggagtgcagcaaaagccgc      150
                                           0
HAL3      1
CKS1      151 ggatgggtacattacgcggttcacgcacctgagccgcacataatgctatt      200
                                           0
HAL3      1
CKS1      201 caggaggcctcttaactatcagcagcagcaggagaatcaagctcagaaca      250
                                           0
HAL3      1
CKS1      251 tgcttggttaagtgaatc
                                           267
                                           .|||||.
HAL3      1 atgaatatggaagtggatccagtaacaaggaaacccctcgta      40
                                           267
CKS1      268
                                           267
HAL3      41 tcttactagctgcaagtgaagtggtggttcaattaagttcagtaattctc      90
                                           267
CKS1      268
                                           267
HAL3      91 tgccattgtttctcagaatgggctgaagtcaaaagccgtcgttcaaaatc      140
                                           267
CKS1      268
                                           267
HAL3      141 atctctcaatttcgttgataaaccttctctcctcagaatgtgactctct      190
                                           267
CKS1      268
                                           267
HAL3      191 atacagatgaagatgaatggctcagctggaacaagattgggtgatcccggt      240
```

## EMBOSS GUI v1.13: output from needle

CKS1	268		267
HAL3	241	cttcatatcgagctcagacgctgggctgatgttatgatcattgctccttt	290
CKS1	268		267
HAL3	291	gtctgctaacacattagccaagattgctggggttatgtgataatctat	340
CKS1	268		267
HAL3	341	tgacatgtatagtaagagcatgggattatagcaaaccgttgtttggtgca	390
CKS1	268		267
HAL3	391	ccggcgatgaacactttgatgtggaacaatcctttcacagaacggcacct	440
CKS1	268		267
HAL3	441	tgtcttgcttgatgaacttggaatcacccctaattcctcccatcaagaaga	490
CKS1	268		267
HAL3	491	aactggcctgttgagactacggtaatggcgcaatgctgagccttctctg	540
CKS1	268		267
HAL3	541	atttattccactgttagactgttctgggagtcacaagctcgtaaacaaag	590
CKS1	268		267
HAL3	591	agatgggaaccagt	603

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